SAMSUNG MEDICAL CENTER

2010 춘계 심장학회
Debate in Congenital Heart Disease

TRIAL OF PULMONARY VASODILATOR IN A FONTAN PATIENT WITH PULMONARY HYPERTENSION

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Case

- 12^M
- s/p Fontan
- NYHA class II (worse than before)
- intermittent History of atrial flutter
- exercise CP test: VO2max -2/3 of normal
- systemic venous pressure 15mmHg
- liver cirrhosis on abdominal CT

Trial of pulmonary vasodilator??

What should be taken into considerati on before prescribing new drug ?

- Will it work for this patient?
- Will it be OK ?
  - Effect/side effect
  - Drug interaction
  - Cost-benefit
- How long ?

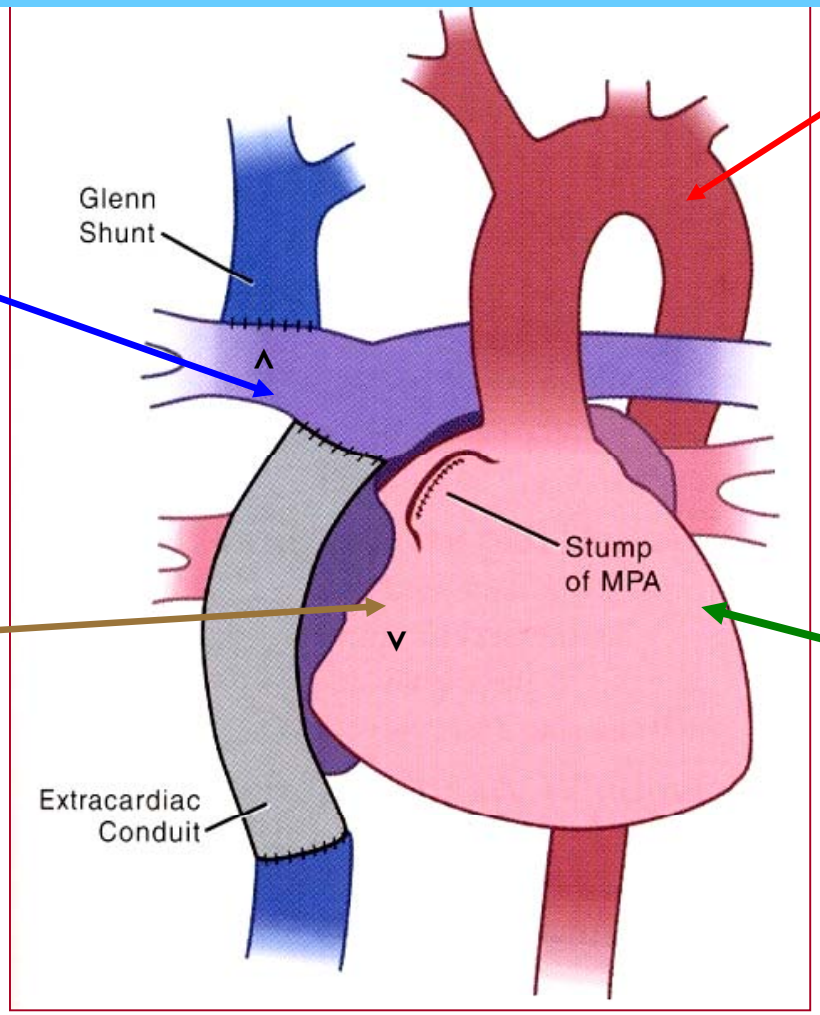
intermittent History of atrial flutter
exercise CP test: VO2max -2/3 of normal
systemic venous pressure 15mmHg,
liver cirrhosis on abdominal CT

Pulmonary vascular resistance

systemic venous pressure 15mmHg,

Rhythm disturbances

intermittent History of atrial flutter



liver cirrhosis on abdominal CT

Systemic vascular resistance

Ventricular function

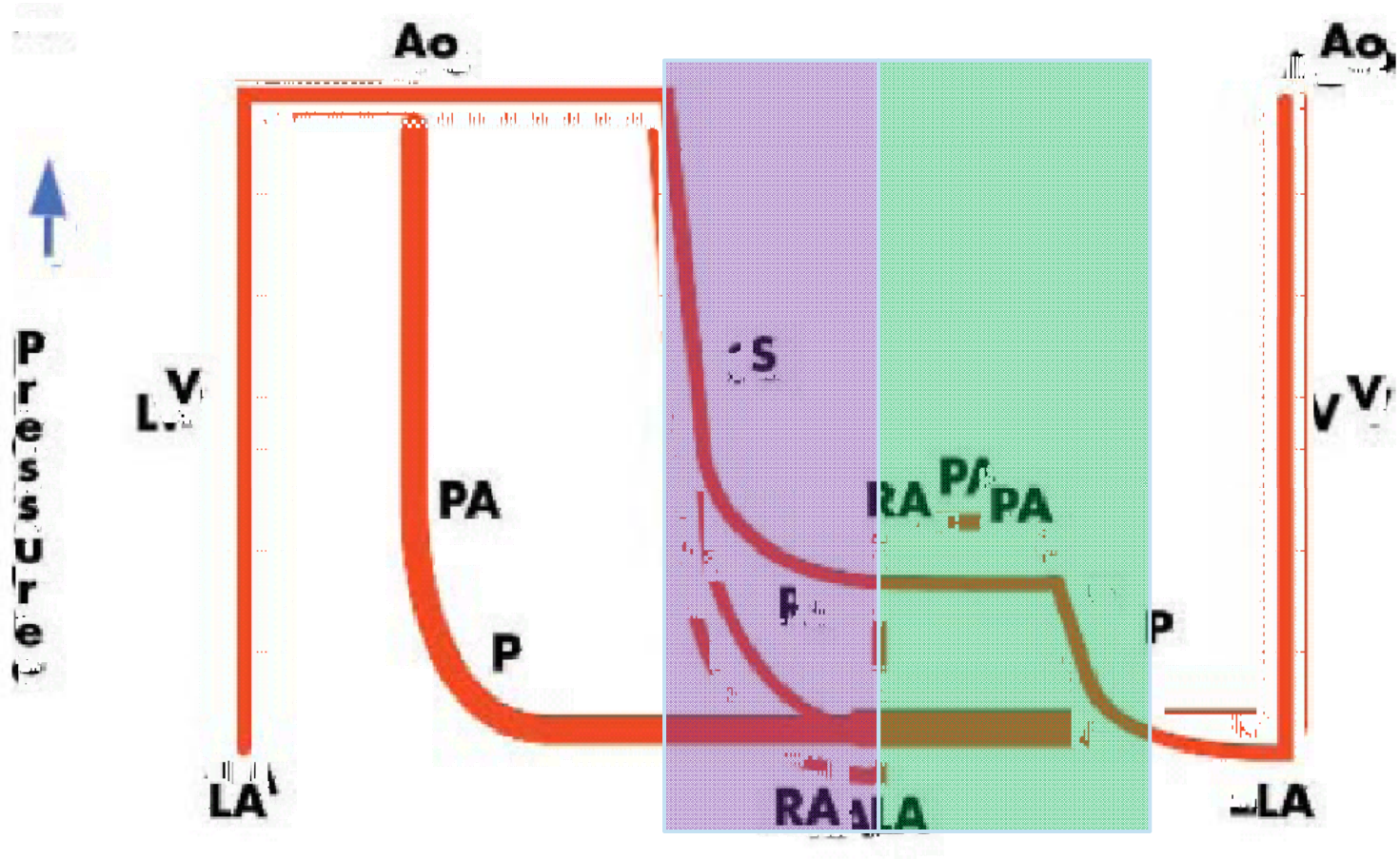
exercise CP test: VO2max -2/3 of normal

WHAT else should be checked?

1. Pulmonary vasculature & Fontan pathway
2. Collateral vessels
3. Fenestration
4. Atrial function
5. Ventricle function
6. Systemic vasculature
7. Thromboembolism
8. Other problems

Correctable or not

The change of circulation in Fontan



Basal Pulmonary Vascular Resistance and Nitric Oxide Responsiveness Late After Fontan-Type Operation

S. Khambadkone, MD, MRCP; J. Li, MBBS; M.R. de Leval, MD, FRCS;
S. Cullen, MB, BCh, BaO, FRCPI; J.E. Deanfield, FRCP; A.N. Redington, FRCP

Background—The pulsatile nature of pulmonary blood flow is important for shear stress–mediated release of endothelium-derived nitric oxide (NO) and lowering pulmonary vascular resistance (PVR) by passive recruitment of capillaries. Normal pulsatile flow is lost or markedly attenuated after Fontan-type operations, but to date, there are no data on basal pulmonary vascular resistance and its responsiveness to exogenous NO at late follow-up in these patients.

Methods and Results—We measured indexed PVR (PVRI) using Fick principle to calculate pulmonary blood flow, with respiratory mass spectrometry to measure oxygen consumption, in 15 patients (median age, 12 years; range, 7 to 17 years; 12 male, 3 female) at a median of 9 years after a Fontan-type operation (6 atriopulmonary connections, 7 lateral tunnels, 2 extracardiac conduits). The basal PVRI was 2.11±0.79 Wood unit (WU) times m^2 (mean±SD) and showed a significant reduction to 1.61±0.48 (P=0.016) after 20 ppm of NO for 10 minutes. The patients with nonpulsatile group in the pulmonary circulation dropped the PVRI from 2.18±0.34 to 1.82±0.55 (P<0.05) after NO inhalation.

Conclusions—PVR falls with exogenous NO late after Fontan-type operation. These data suggest pulmonary endothelial dysfunction, related in some part to lack of pulsatility in the pulmonary circulation because of altered flow characteristics. Therapeutic strategies to enhance pulmonary endothelial NO release may have a role in these patients.
(*Circulation*. 2003;107:3204-3208.)

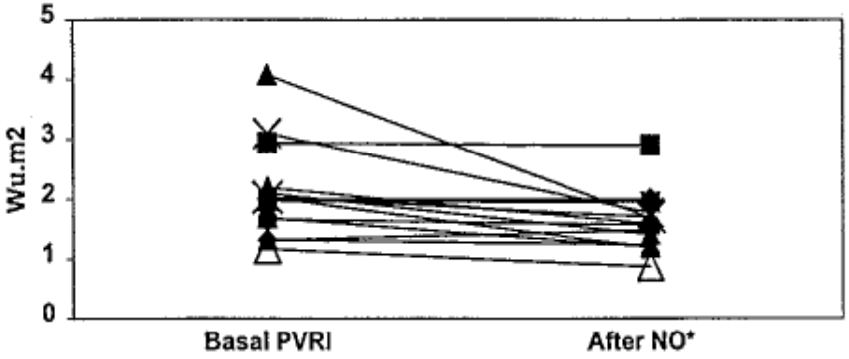


Figure 4. Effect of exogenous NO on PVRI late after Fontan operation. NO caused a significant drop of mean PVRI in the study group (*P=0.016).

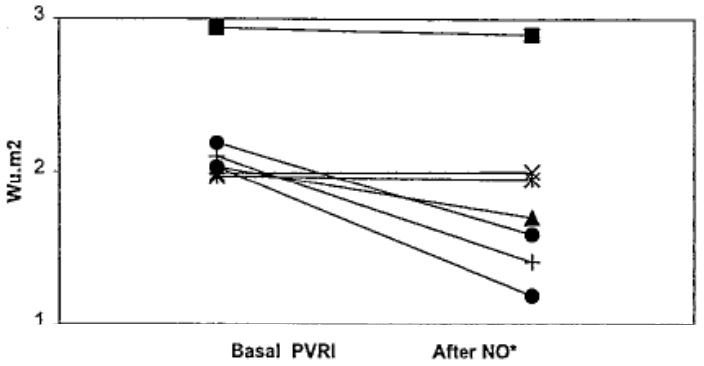


Figure 7. Effect of exogenous NO on PVRI of patients with non-pulsatile flow in the pulmonary arteries. Significant drop of mean PVRI (*P<0.05).

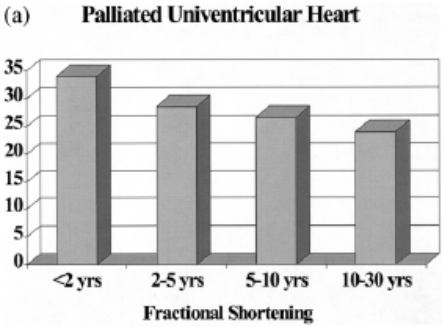
Function of SV

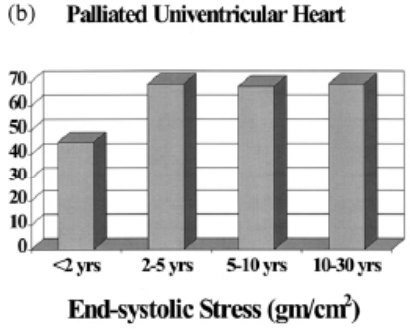
Systolic and diastolic function of the univentricular heart

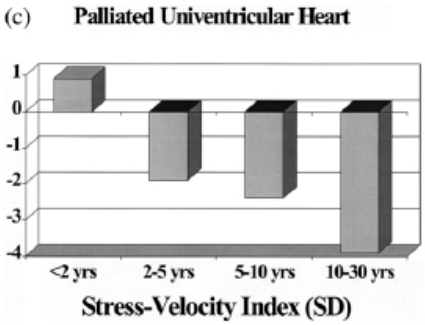
Steven D. Colan*

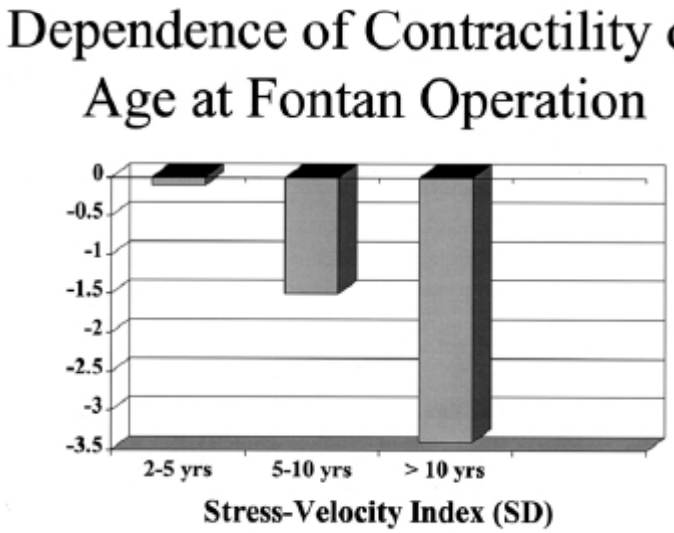
Preload ↓
SVR ↑
Mass:volume ratio ↑

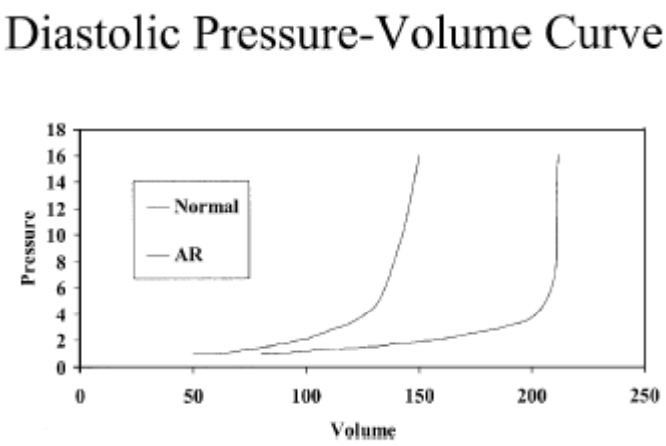
Compliance?
impaired relaxation?











Mechanism of pulmonary HT associated with left heart disease

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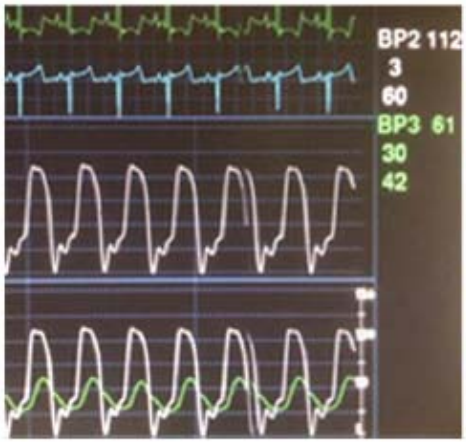
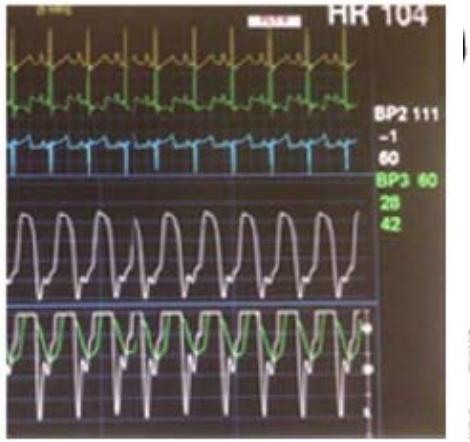
The causes of pulmonary venous hypertension in children.

Large left-to-right shunts (intracardiac or extracardiac)
Arteriovenous malformations
Pulmonary vein stenosis
Obstructed anomalous pulmonary venous return
Conditions with complicated by restrictive or intact atrial septum
Hypoplastic left heart syndrome
Single ventricle with left atriventricular valve stenosis or atresia
Transposition of the great arteries with intact ventricular septum and patent ductus arteriosus
Post Norwood stage 1
Post total cavopulmonary anastomosis with left AV valve stenosis
Small left atrial syndrome
Post repair of total anomalous pulmonary venous drainage
Shone's Syndrome variants
Mitral valve stenosis
Cortriatriatum
Supravalvar stenosing ring
Mitral valve regurgitation especially with a small or noncompliant left atrium
Post supra-annular mitral valve prosthesis
Aortic valve insufficiency
Aortic valve stenosis
Elevated left ventricular end diastolic pressure
Dilated cardiomyopathy
Restrictive cardiomopathy
Hypertrophic cardiomyopathy
Endocardial fibroelastosis especially from congenital left heart obstructive disease
Hypoplasia of the left ventricle
Right ventricular pressure and volume load through ventricular interactions
Left ventricular hypertrophy
Systemic hypertension
Left ventricular diastolic dysfunction
Pericardial effusion or constriction

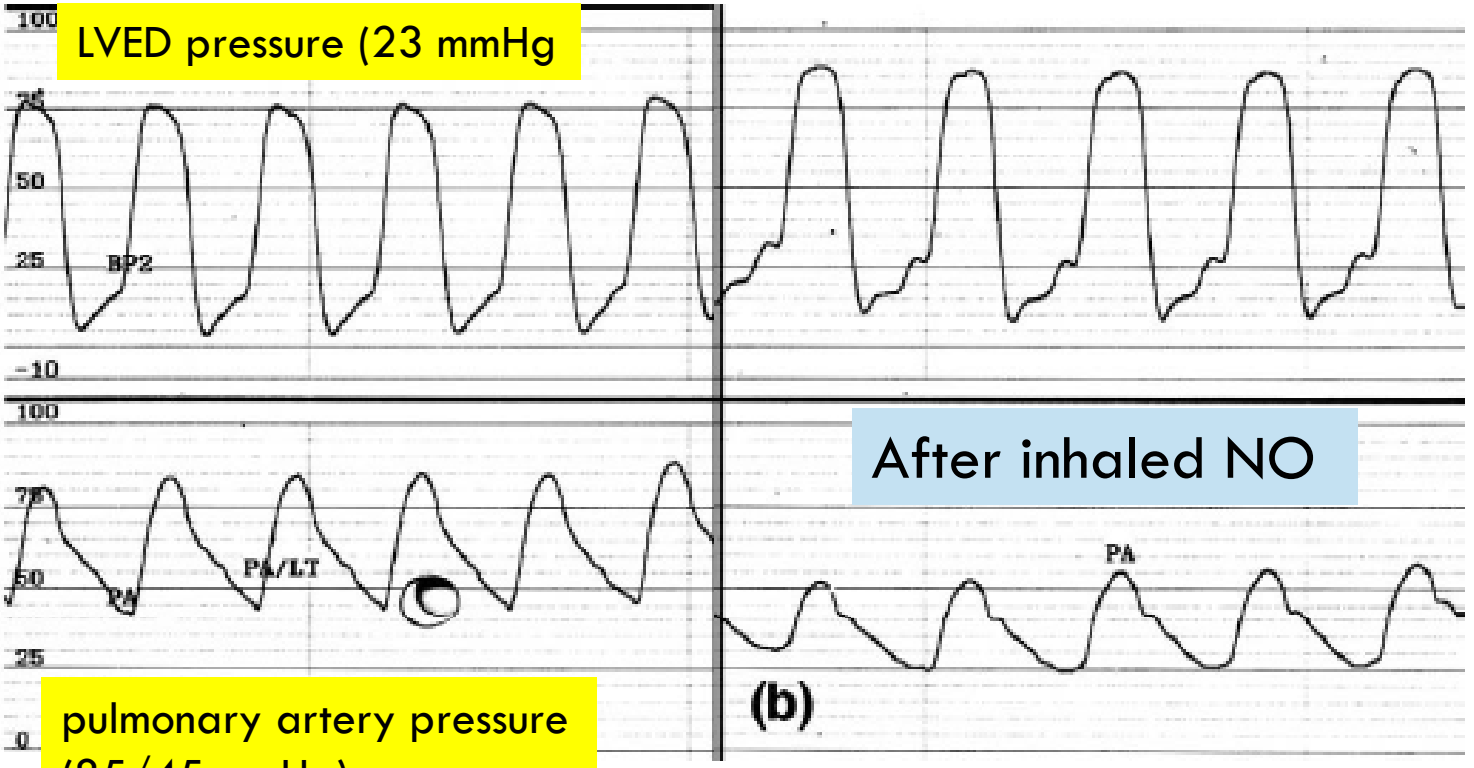
1. passive,
2. reflex vasoconstriction
3. fixed



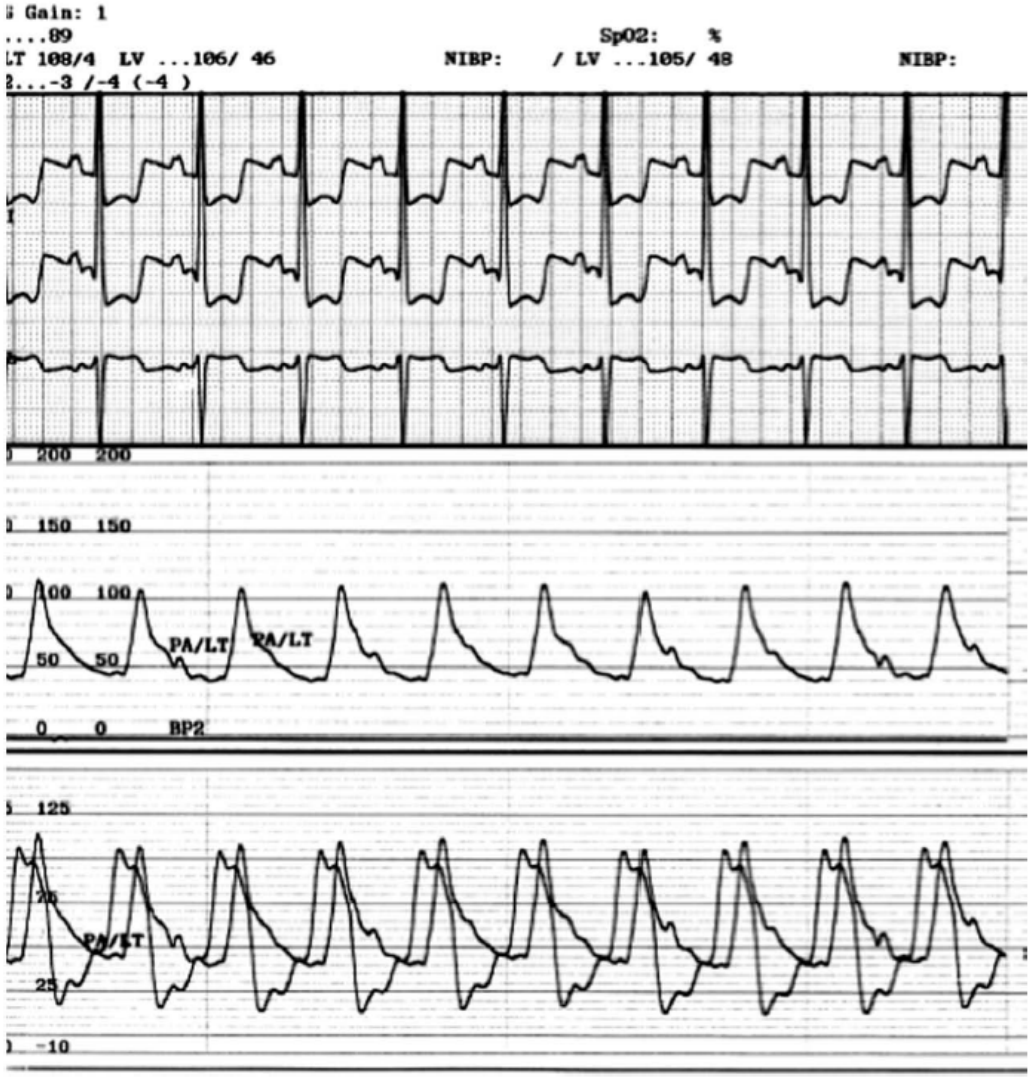


An example of reflex pulmonary vasoconstriction

restrictive cardiomyopathy



An example of fixed pulmonary vascular disease



16-year-old patient born with critical aortic stenosis

PAP = 110/45 mmHg
LVEDp = 25 mmHg
TPG = 46 mmHg
PVRI = 22WUm2.

no change with NO

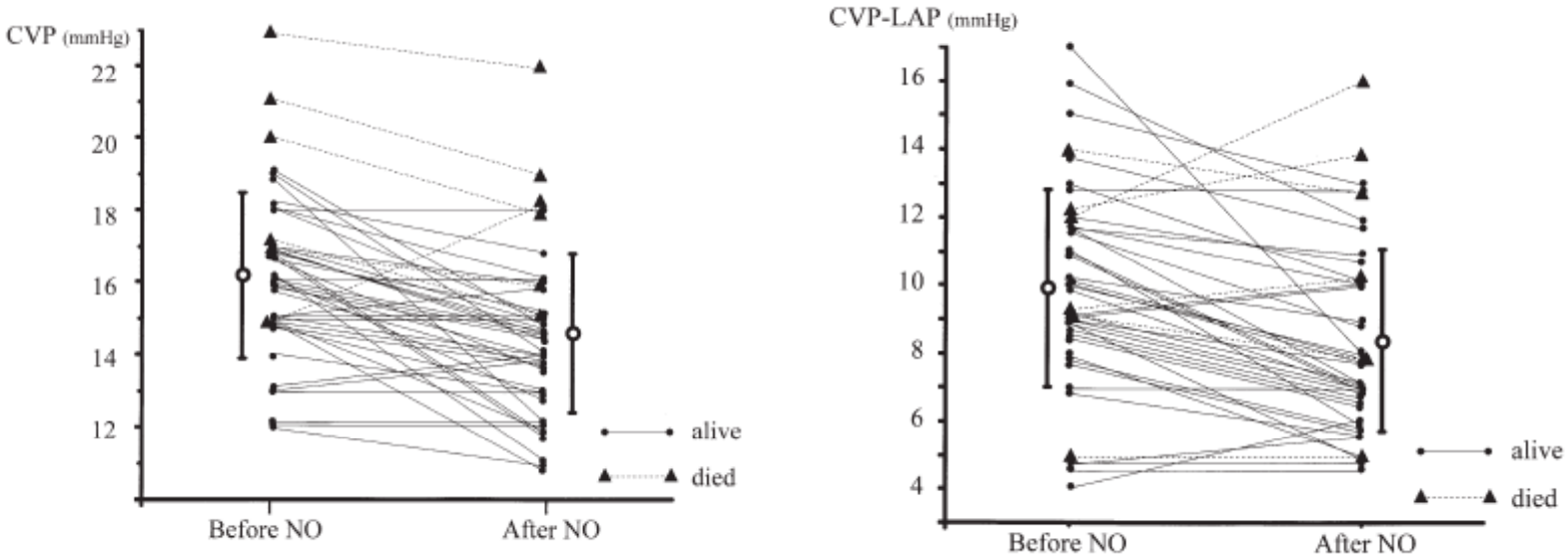
Failing Fontan

-Etiologies of volume retention/ fatigue

- Anatomic/ hemodynamic
  - Right- or left-ventricular dysfunction/outflow obstruction
  - Atrioventricular valve regurgitation
  - Baffle obstruction
  - Pulmonary artery/ vein obstruction: Qp/Qs imbalance
  - ↑ PVR
  - Systemic artery to pulmonary vein, or, systemic artery to pulmonary artery connection
- Arrhythmia
- Systemic venous/ arterial hypertension
- Renal/ hepatic dysfunction/ protein losing enteropathy
- Primary lung disease (restrictive or obstructive)
- Occult infection/ SBE / spontaneous bacterial peritonitis
- Pregnancy
- Acquired co-morbid illness: e.g. endocrinopathy

Inhaled Nitric Oxide Therapy After Fontan-Type Operations

- Naoki Yoshimura, et al. Surg Today (2005) 35:31–35



Bosentan Induces Clinical, Exercise and Hemodynamic Improvement in a Pre-Transplant Patient With Plastic Bronchitis After Fontan Operation

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- Sotiria C. Apostolopoulou, et al. J Heart Lung Transplant 2005;24:1174–6.

Table 1. Clinical, Exercise and Hemodynamic Parameters at Baseline and After 16 Weeks of Bosentan Treatment

Parameter	Baseline	Week 16	Percent change from baseline
WHO functional class	III	II	
Mean pulmonary pressure (mm Hg)	18	15	−17%
Transpulmonary pressure gradient (mm Hg)	8	5	−38%
Mean aortic pressure (mm Hg)	102	92	−10%
Pulmonary flow index (liters/min m^{-2})	3.3	3.6	+9%
Systemic flow index (liters/min m^{-2})	4.8	3.8	−21%
Pulmonary:systemic flow ratio	0.7	0.9	+29%
Pulmonary vascular resistance index (dyne/s cm^{-5})	192	112	−42%
Systemic vascular resistance index (dyne/s cm^{-5})	1,408	1,632	+16%
Pulmonary to systemic vascular resistance ratio	0.14	0.07	−50%
Peak oxygen consumption (ml · kg min^{-1})	21.0	22.4	+7%
Exercise duration (min)	8.5	12.0	+41%
6-minute walk distance (m)	468	505	+8%
Borg dyspnea index	3	2	
Pulse oximetry (%)	90	94	+4%

Transpulmonary pressure gradient = mean pulmonary pressure minus left atrial pressure. WHO, World Health Organization.

Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients

- Alessandro Giardini, et al. European Heart Journal (2008) 29, 1681–1687

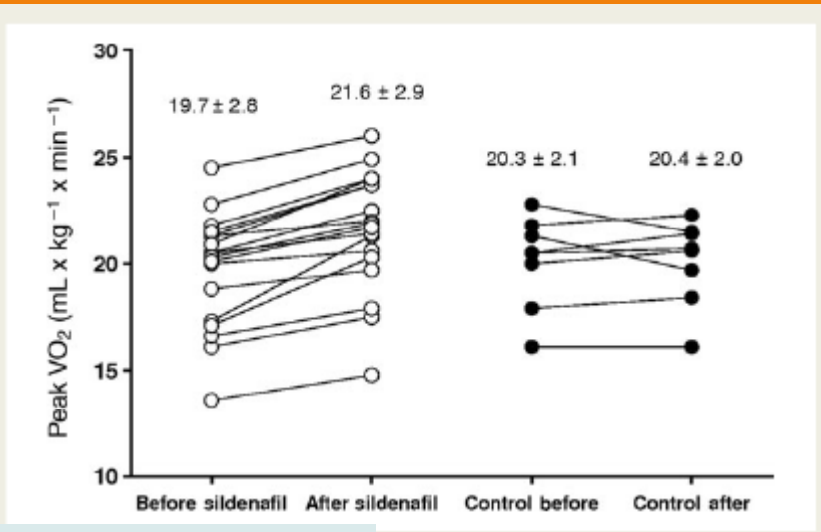


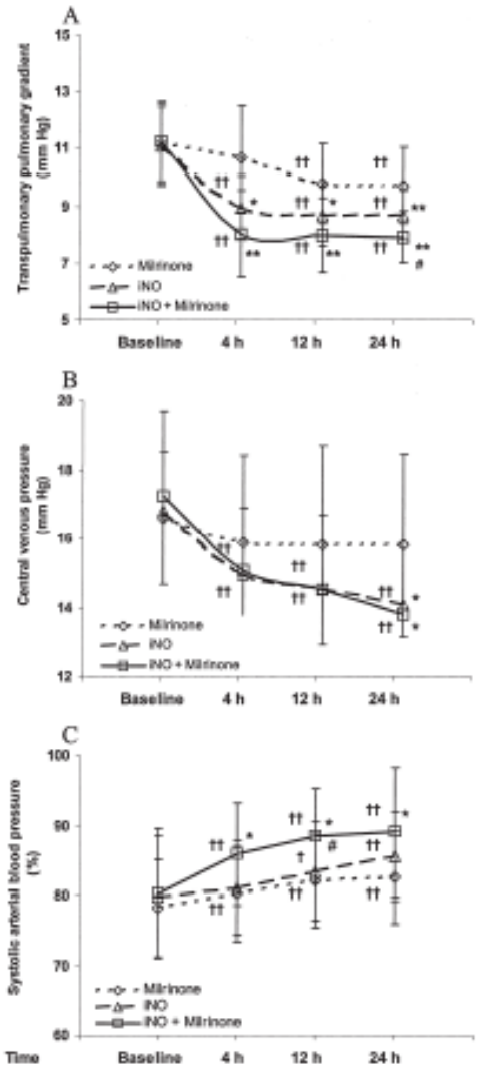
Table 3 Change in cardiopulmonary and haemodynamics variables observed in the sildenafil treatment and in the no treatment arm for exercise test nos 2 vs. 3

Variable	%Δ exercise test nos 2 vs. 3			
	Sildenafil (n = 18)	No treatment (n = 9)	Treatment effect	P
Peak VO_2	9.4 ± 5.2	0.3 ± 4.1	9.1%	<0.05
PBF index				
Rest	28.8 ± 12.2	1.1 ± 3.4	27.6%	<0.01
Peak exercise	11.2 ± 7.0	1.0 ± 3.4	10.2%	<0.05
CI				
Rest	29.0 ± 13.1	1.6 ± 3.7	27.4%	<0.001
Peak exercise	10.0 ± 7.2	0.9 ± 4.3	9.1%	<0.05
SaO_2				
Rest	0.5 ± 1.8	0.1 ± 0.8	0.4%	>0.05
Peak exercise	1.3 ± 2.6	−0.2 ± 1.1	1.5%	>0.05

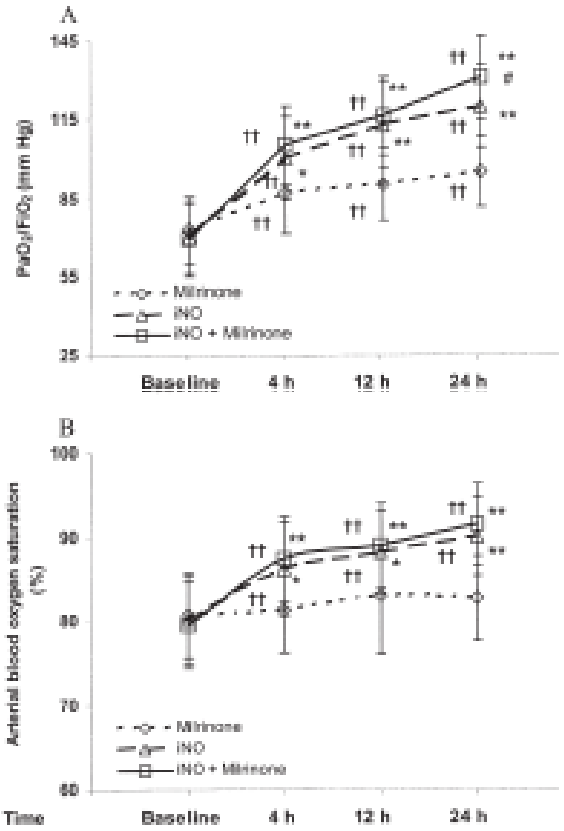
CI, cardiac index; PBF, pulmonary blood flow; SaO_2, arterial oxygen saturation; VO_2, oxygen uptake.

Nitric Oxide in Conjunction With Milrinone Better Stabilized

Pulmonary Hemodynamics After Fontan Procedure



- Jiming Cai, et al. *Artificial Organs,* 32(11):864–869,



Beneficial Effect of Oral Sildenafil Therapy on Childhood Pulmonary Arterial Hypertension

Twelve-Month Clinical Trial of a Single-Drug, Open-Label, Pilot Study

Tilman Humpl, MD; Janette T. Reyes, RN, MN (ACNP); Helen Holtby, MBBS; Derek Stephens, MSc; Ian Adatia, MBChB

Background—Pulmonary arterial hypertension (PAH) is a progressive and fatal disease. Sildenafil is a type 5 phosphodiesterase inhibitor and pulmonary vasodilator. Therefore, we hypothesized that sildenafil would improve distance walked in 6 minutes and hemodynamics in children with PAH.

Methods and Results—After baseline assessment of hemodynamics by cardiac catheterization and distance walked in 6 minutes, we administered oral sildenafil at 0.25 to 1 mg/kg 4 times daily to 14 children (median age, 9.8 years; range, 5.3 to 18). Diagnoses were primary (n=4) and secondary (n=10) PAH. We repeated the 6-minute walk test at 6 weeks and at 3, 6, and 12 months (n=14) and cardiac catheterization (n=9) after a median follow-up of 10.8 months (range, 6 to 15.3). During sildenafil therapy, the mean distance walked in 6 minutes increased from 278±114 to 443±107 m over 6 months (P=0.02), and at 12 months, the distance walked was 432±156 m (P=0.005). A plateau was reached between 6 and 12 months (P=0.48). Mean pulmonary artery pressure decreased from a median of 60 mm Hg (range, 50 to 105) to 50 mm Hg (range, 38 to 84) mm Hg (P=0.014). Median pulmonary vascular resistance decreased from 15 Wood units m^2 (range, 9 to 42) to 12 Wood Units m^2 (range, 5 to 29) (P=0.024).

Conclusions—Oral sildenafil has the potential to improve hemodynamics and exercise capacity for up to 12 months in children with PAH. Confirmation of these results in a randomized, controlled trial is essential. (***Circulation*. 2005;111: 3274-3280.**)

Mechanism of pulmonary HT in this Fontan case

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- Endothelial dysfunction related to the absence of pulsatile flow – PROBABLY

Reversible or not

- Arrhythmia – Partly contributing
- Ventricle dysfunction - POSSIBLY
  systolic / diastolic
- Volume overload - MAYBE
  systemic to pulmonary collaterals
  hepatic / renal

Correctable

Yes, I will ….

FIRST

CATH & Angio

+ CT /MRI

VASODILATOR TEST

SECOND

FIND CORRECTABLE FACTORS

TRY PULMONARY VASODILATORS

LAST

CHECK PAP / PVR / CO / PE

CHECK EFFECT/ SIDE EFFECT OF DRUG